

**Response Under 37 C.F.R. 1.116 - Expedited Procedure**  
**Examining Group 1646**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE **RECEIVED**

In re Application of: Jennifer L. Hillman

OCT 08 2003

Title: TIMM8b-RELATED PROTEIN

TECH CENTER 1600/2900

Serial No.: 09/781,117

Filing Date: February 08, 2001

Examiner: Chernyshev, O.

Group Art Unit: 1646

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Sir:

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1. Return Receipt Postcard; and
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Respectfully submitted,

INCYTE CORPORATION

Date: October 1, 2003

David G. Streeter

David G. Streeter, Ph.D.

Reg. No. 43,168

Direct Dial Telephone: (650) 845-5741

**Customer No.: 27904**

3160 Porter Drive  
 Palo Alto, California 94304  
 Phone: (650) 855-0555  
 Fax: (650) 849-8886



Docket No.: PC-0034 US

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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**REPLY BRIEF**

Sir:

**I. INTRODUCTION**

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated August 12, 2003 ("the Examiner's Answer") in the above-identified application (the Hillman '117 application). With reference to Applicants Brief on Appeal filed May 22, 2003, the Examiner stated that with respect to the following sections of the brief:

- (1) **Real Party of Interest**
- (2) **Related Appeals and Interferences**
- (3) **Status of Claims**
- (4) **Status of Amendments After Final**
- (5) **Summary of the Invention .**
- (6) **Issues**

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**(7) Grouping of Claims**

**(8) ClaimsAppealed**

Applicants statements and summaries recited above are correct.

In addition, in the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of the claims on appeal under 35 U.S.C. § 101 on the grounds that the claimed invention is not supported by a specific, substantial and credible asserted utility, or well-established utility;

(2) maintained the rejection of the claims on appeal under 35 U.S.C. § 112, first paragraph for alleged lack of enablement because of the invention's alleged lack of utility.

**II. UTILITY REJECTIONS**

**A. Introduction**

The Examiner has maintained the rejections under 35 U.S.C. §§ 101/112 first paragraph for an alleged lack of a specific and substantial asserted utility or a well established utility on the grounds that "the instant application does not disclose a specific biological role for this protein or its significance to a particular disease, disorder or physiological process" (Examiners' Answer, at page 3). The Examiner quotes *Brenner v. Manson* and states that the instant claims are drawn to an isolated nucleic acid molecule and the protein encoded thereby of as yet undetermined function or biological significance. The Examiner then reiterated previous arguments alleging to the unpredictability protein function based on similarities in structure and referencing previously cited literature in support of this contention (see, in particular, Skolnick et al. and Bork et al.). The Examiner concluded stating that the instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the instant nucleic acid and encoded protein is associated with any diseases or disorder.

**B. Responses to Specific Arguments by Examiner**

**1. Use of the claimed invention in toxicology testing and drug discovery confers a well-established utility on the claimed invention**

The Examiner made various statements in the Examiner's Answer refuting Appellants

assertion in the Brief of the claimed invention's use in toxicology testing and drug development. Each of these statements will be addressed in turn.

**A. Applicants references in support a well-established utility for the claimed invention in expression profiling for toxicology testing and drug discovery do not support such an assertion (Examiner's Answer, at pages 8-10).**

The Examiner stated that literature reviews cited by applicants as describing the state of the art on the use of expression profiling in toxicology testing and drug discovery, in fact, support the Examiners' contention that such use is insubstantial and requires further experimentation.. In particular, the Examiner noted that Rockett et al., cited by appellants at page 12 of the brief, supported the Examiners' contention that "further experimentation to determine the properties of that which is being claimed" is required, and that Lashkari et al.(page 12 of the brief) teaches that "Experimental analysis must be performed to thoroughly understand the biological function of a gene product" and that "sequences of unknown function or significance are used in such strategies to learn more about the sequences themselves and the genes they represent".

Examiners' Answer at pages 9-10.

The Examiners' position again appears to stem from an allegation that any useful information from gene expression can only be obtained when the "biological function" of the gene product is known and a specific interpretation of any result from an expression profile experiment can be made. This issue was specifically addressed at § III.A of the brief. Appellants recognize that any experimental result necessarily leads to further experimentation, but that such further experimentation is not necessary to provide a "real-world benefit" in this case. The Examiners' Arguments ignore the "real-world benefit" for gene expression profiling exemplified by statement in Rockett et al. (at page 12 of the brief) that :

--- the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

It is thus the pattern of a gene expression profile that provides a specific benefit and does not require a specific interpretation of the result "for each individual member of the array" (Examiners' Answer, bottom of page 10. Further, the Examiners' statement that such a utility "is

nonspecific and would apply to virtually every member of a general class of materials, such as proteins or DNA” does not negate the “real world benefit” described above. Appellants have further noted, specifically at page 22 of the brief, that where courts have found a utility to be to “general” has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. This is clearly not the case described above.

**B. This is a utility which is nonspecific and would apply to virtually every member of a general class of materials, such as proteins or DNA (i.e., is not “specific” to the products claimed, (Examiner's Answer, Page 10).**

The issue of what constitutes a sufficiently “specific” utility to the claimed subject matter has been addressed in detail in the Brief at § IV, pp. 21-23. As stated at p. 16 of the Brief, the law has never required that a “specific” utility be one that is “unique” or “particular” to the claimed subject matter, such as the Training Materials for the Revised Utility Guidelines appear to require, and the Examiner has so stated, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. The fact that the use of the claimed polynucleotides in toxicology testing and drug discovery confers “specific benefits” to the public is discussed in detail in the Brief in § II.A, at pp. 8-13. The fact that a utility may be shared by a broad class such as all nucleic acids or genes, does not negate it as a valid utility, and no such requirement is found in the law. Appellants further note that the claimed invention is not just “any” DNA, but an expressed, human DNA clearly useful for human, gene expression profiling as described. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. This is clearly not the case with the present invention for all the reasons discussed in the Brief on Appeal.

**2. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility**

The Examiner continues to contend that appellants assertion of TRP of the instant invention as a TIMM8b related protein does not confer a well established utility on the claimed invention because “structural similarities are not equivalent to direct extrapolation of biological

functions" (Examiners' Answer, at page 11). While not necessary to fulfill the requirements for utility of a claimed polynucleotide, the identification of the polypeptide encoded by the claimed polynucleotide as functionally related to human TIMM8b, with "reasonable probability" has been discussed at length in section II.C, pages 15-16 of the brief. In particular, it was noted that in addition to an overall sequence identity of 85% with human TIMM8b, the two proteins are actually 100% identical over all but the N-terminal 15 amino acids, and including an important sequence motif characteristic to the DDP/TIM family of mitochondrial proteins. Given this level of sequence identity and specific sequence motif characterization, the probability that the polypeptide encoded by the claimed polynucleotide is a functional as well as structural homolog of TIMM8b is, accordingly, very high.

**5. Applicants have asserted a utility for the claimed invention that is completely independent of any knowledge regarding the encoded proteins' function**

The Examiner continues to ignore applicants asserted use for the claimed polynucleotides in the diagnosis of certain cancers based on differential expression in, particularly, breast cancer, ovarian cancer, and kidney cancer based on specific evidence from Northern tissue analysis presented in Table 2 of the specification. The Examiner continues to contend that the data of Table 2 "is not definite". See Examiners' Answer, at page 14. The Examiner contends that the data does not allow a skilled artisan to clearly distinguish between normal and cancer tissue in the instant case.

The significance of the data in Table 2 in support of the use of the claimed polynucleotide in diagnosing breast, ovarian, or kidney cancers based on differential expression in these conditions relative to normal tissue was explained, in detail, in the initial response to an Office Action filed 10/10/2002 and in the brief at pages 20-21. Specifically, this data showed the results of a search of the Incyte LIFESEQ database of cDNA libraries (containing at that time, nearly 1300 libraries; see Table 1) by individual tissue category for the most abundant expression of the polynucleotide. As described in the specification at page 33, Example VIII, particular significance was given to libraries showing "overexpression" of the gene, i.e., an abundance of 2 or more transcripts/library. The results of this analysis, given in Table 2 showed that in breast, ovary, and kidney tissues, those cDNA libraries exhibiting these properties were all obtained

from cancerous tissues. More significantly, beyond the obvious fact that any normal cDNA libraries from those sources by necessity must express the polynucleotide at a lower level, at least two of the four libraries, BRSTTUT14 and KIDNTUT15, were matched with normal tissue libraries from the same patient, in which expression was undetectable. An additional kidney tumor library, KIDNTUT14, though not “overexpressing” the polynucleotide was also matched with a normal tissue library where expression of the polynucleotide was, again, undetectable. Thus differential expression of the claimed polynucleotide in specific cancers was characterized either by the presence or absence of the polynucleotide in the pathological versus the normal condition, or by a measurable degree of differential expression in one condition versus the other. Appellants therefore, again, submit that such evidence provides a “substantial likelihood” for utility of the claimed polynucleotide in the detection and diagnosis of these conditions.

**4. The Examiner’s Answer is Based on Flawed Assumptions about the Legal Standard for Utility**

In the face of Appellants’ demonstration of numerous disclosed and well-established utilities for the claimed polynucleotides, the Examiner’s Answer does not offer any facts or sound scientific reasoning as would be required to overcome the presumption of utility that must be attributed to the claimed invention as a matter of law. For example, the Examiner’s Answer has no answer for the disclosed utilities of the claimed polypeptides in gene expression monitoring applications that are discussed under Issue I. of the brief.

The Examiner has not and cannot provide **any** evidence tending to show that a person of ordinary skill in the art could not achieve the disclosed utilities, or indeed that any experimentation whatsoever would be required to put the claimed invention to beneficial use. And the Examiner’s Answer fails to address the Appellants’ overwhelming evidence demonstrating not only that persons of ordinary skill in the art recognize the utility of inventions such as those claimed, but also that the likelihood that the claimed invention would achieve those utilities is far beyond substantial.

Apart from ignoring the presumption of utility and the Examiner’s burden to overcome it, the Examiner’s Answer ultimately is based on two flawed assumptions. They are

- i. the claimed invention cannot be proven to be useful until the biological roles or functions of the polypeptides or polynucleotides also are proven; and
- ii. the *Brenner v. Manson* case somehow supports the Examiner's position in the present situation

Examiners' Answer, at pages 13-14

Both of these assumptions are incorrect.<sup>1</sup>

**1. The precise biological role or function of an expressed polynucleotide or polypeptide is not required to demonstrate utility**

Rather than responding to Appellants' evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not specific, substantial, and credible utilities (Examiner's Answer at page 3). The Examiner is incorrect both as a matter of law and as a matter of fact.

The basis of the Examiner's argument is that, without information as to the precise biological role of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polypeptides to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide an "interpretation for the result" generated in any given expression analysis (Examiner's Answer, page 10).

It may be that such "interpretations" and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re*

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<sup>1</sup> It is respectfully submitted that the entirety of the Examiner's alleged rebuttal of Appellants' arguments and reasoning in the Examiner's Answer are based on these incorrect assumptions. Nevertheless, to the extent that Appellants do not specifically rebut these points on a line-by-line basis, this is not to be construed as acquiescence to their veracity, and Appellants do not waive the right to rebut them individually at any later point in the proceedings.

*Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an “identifiable benefit” in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999)<sup>2</sup>. If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt that the present invention easily meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called “throwaway” utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, e.g., it hybridizes near a disease-associated gene or it has gene-regulating activity.

Biological role or function is, instead, merely one factor that can be relevant in demonstrating whether there is a “substantial likelihood” a claimed invention can achieve the identified benefits. It may be particularly helpful in those cases where it is necessary to prove that the identifiable benefit of one biological composition can be imputed to another. In these cases, see, e.g., *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995), because there is no direct evidence that the biological composition can achieve any given utility, knowledge of biological function can be used to prove a “substantial likelihood” of utility indirectly, by association. Biological function serves as a link between a compound whose utility

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<sup>2</sup> *Juicy Whip* states:

An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

otherwise would be unknown and another compound having known utility. If, for example, a prior art biological composition is known to be a target in the treatment of disease, one way the applicant can prove utility is by demonstrating that the claimed invention is substantially likely to share the utility for disease treatment because it also shares a biological role with the prior art composition.

But in other cases, such as this one, proof of biological function is not necessary. In those cases, the evidence already is sufficient to show that there is a substantial likelihood that the claimed invention produces the alleged benefit. The claimed invention has a known utility whether or not it can be linked (through biological function) with some other composition.

By implicitly requiring knowledge of biological function for any claimed polynucleotide or polypeptide, the Examiner has, contrary to law, elevated what has long been acknowledged to be an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

## **2. Assignment to a family whose members are useful establishes utility**

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the transcriptional regulatory molecules family, the Examiner refused to impute the utility of the members of the DDP/TIM family of mitochondrial proteins to TRP. The Patent Examiner takes the position that, unless appellants can identify which particular biological function within the class of DDP/TIM molecules is possessed by TRP, utility cannot be imputed. To demonstrate utility by membership in the class of DDP/TIM molecules, it appears the Examiner would require that all DDP/TIM molecules possess a “common” utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a “general” class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g., Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses TRP as if the general class in which it is included is not the DDP/TIM molecules, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these “general classes” may contain a substantial number of useless members, the DDP/TIM molecules family does not. The DDP/TIM molecules family is sufficiently specific to rule out any reasonable possibility that TRP would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the DDP/TIM molecule class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a “substantial likelihood” that the TRP encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide also is useful.

### **3. The Examiner’s reliance on *Brenner v. Manson* is misplaced**

This is not a case in which biological function is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention is disclosed in the Hillman ‘117 application to be useful as a tool in a number of gene expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function of the claimed polynucleotides is superfluous information for the purposes of establishing utility.

The uncontested fact that the claimed invention already has a disclosed use as a tool in then available technology (such as gene expression profiling) distinguishes it from those few claimed inventions found not to have utility. In each of those cases, unlike this one, the person of

ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases, *Brenner v. Manson*, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect.

*Brenner* concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the SEQ ID NO:2 polynucleotide is an expressed polynucleotide that was disclosed to be useful in the Hillman '117 application for many known applications involving gene expression analysis. Its utility is not a matter of guesswork. It is not a random DNA or polypeptide sequence that might or might not be useful as a scientific tool. Unlike the steroid in *Brenner*, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions.<sup>3</sup>

And, the utilities disclosed in the application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug.

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<sup>3</sup> While not necessary to reverse the Examiner's rejections, it is appropriate to point out that because the SEQ ID NO:2 polynucleotide is an expressed human polynucleotide, it is highly more likely than not that it belongs to the class of molecules that have been pre-selected by nature to be useful.

Accordingly, in this case, biological function is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function, as the evidence presented by the Appellants demonstrates. Given that the claimed invention has disclosed and well-established utilities, the Appellants need not demonstrate utility by imputation.

In the end, the Examiner has failed to recognize that new technologies, such as those involving the use of cDNA microarrays to conduct gene expression analyses, have made useful biological molecules that might not otherwise have been useful in the past. *See Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polypeptide or polynucleotide could be usefully employed without further research. It has created a need for new tools, such as the claimed polypeptides, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and **real-world benefits** to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

### **III. ENABLEMENT REJECTIONS**

#### **A. To the Extent the Rejection of the Claimed Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.**

The rejection set forth in the Examiner's Answer is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons. The Examiner has not presented any evidence in support of the allegation (at page 8 of the Examiner's Answer) that, in the face of the well-established and asserted utilities for the claimed invention, the skilled artisan would require undue experimentation to practice the invention.

**IV. CONCLUSION**

For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

**This brief is enclosed in triplicate.**

Respectfully submitted,  
INCYTE GENOMICS, INC.

Date: October 1, 2003



David G. Streeter  
Reg. No. 43,168  
Direct Dial Telephone: (650) 845-5741

Customer No.: 27904  
3160 Porter Drive  
Palo Alto, California 94304  
Phone: (650) 855-0555  
Fax: (650) 849-8886